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October 2, 2024

VIA ECF
Honorable Renée Marie Bumb
United States District Court
Mitchell H. Cohen Building and
U.S. Courthouse
Courtroom 3D
4th and Cooper Streets
Camden, New Jersey 08101

Re: *In re Valsartan, Losartan, and Irbesartan Products Liability Litigation*, MDL No. 19-2875 (RMB)

Dear Chief Judge Bumb:

Please accept this letter brief on behalf of the Plaintiffs in response to the Defendants' submission with regard to testimony they assert implicates general causation in the upcoming trial.

In summary, causation of physical injury is not an element of any claim in an economic loss trial, nor is it an element or consideration in awarding damages. The recall and the concessions by all Defendants that they could not sell the NDMA and NDEA contaminated pills were predicated only on the unacceptable risk, not on any

finding or assumption that the contamination would cause cancer, and the jury's consideration of value must be framed in the context of the unacceptable risk rendering the pills adulterated and non-saleable. That is because the regulatory standards are framed in terms of risk only. Based on this, general causation should not be inserted into the trial, and the Court should give a limiting instruction as illustrated below so that the jury will be guided on the evidence and questions to be considered and answered.

The Defendants mischaracterize the deposition excerpts identified in their submission. The excerpts quote regulatory terms and standards that address the concept of unacceptable risk, they are not statements of causation. The language that the defense focuses on is the core language of the regulations/guidances/internal SOPs addressing the risks of nitrosamine impurities in drugs. Causation is a higher standard than risk, and inapplicable in this trial, and it would be misleading and unduly prejudicial to inject causation of cancer into the trial.

The Court correctly pinpointed the difference between regulatory risk and general causation, and precluded general causation from the trial, during the July 23, 2024 case management conference:[1]

[1] In reliance on the Court's ruling on July 23, 2024, Plaintiffs removed extensive general causation testimony from the designations.

CHIEF JUDGE BUMB: **It's whether or not the presence of this carcinogen is enough to -- is enough to present a risk. Not whether it causes it, but is enough to present an unacceptable risk. Not whether it causes it or not.** But is it really a risk worth taking?

So, you know, the way I think of it is -- you know, I know it's not an FDA, it must be the Consumer Protection Bureau, whatever, whoever. If -- I mean, if they take a – it used to be the chocolate eggs with the toy inside.

* * *

MS. LOCKARD: Well, and that is, I think, a way that could be presented. It's not -- we're not asking whether it actually caused cancer in anyone. But we do have to quantify the risk in a way.

I mean, the worthlessness piece of it is, it is the safety profile of the drug. And, you know, in order for us to be able to talk about whether the drug is safe, is it effective, was it worth anything, would anybody pay money for this, did anybody pay money for this, you have to look at those issues related around the risk of cancer.[2]

The alternative is if they just want to say --

CHIEF JUDGE BUMB: No, I don't think so. Sorry to interrupt. But I don't think so. I think that if the studies

[2] This part of defense counsel's argument highlights the fallacy in the defense's approach, which is merely theoretical and untethered from reality. Defense counsel suggested that if the contamination did not create a significant risk of cancer the efficacy would outweigh the risk, and a patient would see value and buy the pills. The reality is that due to the defined risk in regulatory law the pills could not be sold (as admitted by all Defendants) and no patient would ever have the opportunity to weigh the benefit and risk as suggested.

show that you shouldn't have any of this present, then you shouldn't. If there's studies that show, well, it's okay if you have just, you know, a minimum, whatever, a trace, whatever, then it's okay. That's -- that's the case. Not whether or not, well, if you do have this, it's going to cause cancer, it might cause cancer. It's either what the studies show. The studies show you shouldn't have any or the studies show it's okay to have just a little. That's what it is. Not whether or not if you have just a little whether it causes it or not. **That's -- now we're getting into an area where we shouldn't be getting into.**

So I think we have to limit what goes before the jury.

* * *

CHIEF JUDGE BUMB: **You can present studies that say that small doses don't present an unacceptable risk. But you cannot talk about: Because it causes cancer, et cetera. Because that's not necessary to this case.**

You could present evidence that says there should be no contaminants, period. You can present evidence that says it's okay to have, you know, a trace or whatever percentage it is, period. But you can't go into: And the reason why it's okay is because they don't find that it causes cancer, whatever, no. That's not in the case.

* * *

CHIEF JUDGE BUMB: Which is why I think we are arguing over something that I don't think we need to be arguing about, because **it seems to me that once it was known that NDMA was present, everyone agreed you couldn't sell it.**

> **Now, the argument is going to be, well, what about pre-recall, were they entirely worthless? And I think for the plaintiff to say, yes, they were because they contained the contaminant, the plaintiff can argue that.**
>
> **The defendants can say, there's literature out there that would say that, you know, if it's just, you know, a smallest of percentage, it's -- it's still acceptable, it's not worthless, then they can do that. But it can't delve into "because it doesn't cause cancer or the risk of cancer." You can't delve into that.**

(7/23/24 Tr., 212:10-18, 213:7-214:7, 215:20-216:4, 218:15-219:3).[3]

The Court's analysis is consistent with the testimony from the parties and their contemporaneous communications about the recall, confirming that the contaminated drugs could not be sold because of the risk posed by NDMA and NDEA. Actual causation of cancer was not necessary or even implicated in the question of whether the pills could be sold. Accordingly, the economic loss claim is predicated on the unacceptable risk that rendered the drugs non-saleable. For

[3] There are no "studies" addressing the amount that was permitted from a regulatory standpoint. The subject is controlled by the applicable regulatory guidances, for example ICH Q3A, the 2008 FDA Guidance regarding genotoxic impurities in drugs, the internal ZHP SOP addressing genotoxic impurities, and others. Those are the rules that supply the framework within which the risk is evaluated and deemed acceptable or unacceptable. And the FDA ultimately set limits after the disclosure of the contamination, which are exceeded by all of the contaminated valsartan at issue.

example, ZHP's press release announcing and explaining the reason for the recall included language mandated by the FDA: the contamination presented an "**unacceptable carcinogenic risk to the intended patient population**." This notwithstanding that in the next sentence ZHP stated that as of the date of the recall there had been **no reports of adverse events related to the contamination**. (SOLCO00024231 (Ex. 1 hereto); SOLCO00024226 (Ex. 2 hereto)). Thus, "unacceptable risk," is the terminology that is relevant and applicable here, as found by the Court at the July 23, 2024 conference.

The Defendants were legally required to know and comply with the regulatory standards that controlled, and **the Court should not allow Defendants to reference or rely on a higher causation standard that was not applicable**. Injecting considerations of dose and causation of cancer will only distract, confuse, and mislead the jury into focusing on concepts and arguments that are legally irrelevant, and questions that won't be asked of the jury at this trial. On the other hand, causation will be an issue tried in the personal injury/cancer cases.

Accordingly, the most appropriate way to address this issue is a jury instruction from the Court, explaining that the jury is considering the concept of risk in a regulatory context, and not medical causation, and to consider the evidence accordingly. Plaintiffs propose the following instruction:

> During the course of the trial you will hear/have heard terms that address the concept of risk when talking about the contamination of the at-issue valsartan containing drugs. Those terms include, for example, genotoxic, mutagenic, probable human carcinogen, carcinogenic risk, and unacceptable carcinogenic risk. Those, and similar terms you will hear during the trial are relevant to your understanding and consideration of the materiality of the risk resulting from the actions by the Defendants, in manufacturing, marketing, and selling the pills contaminated with NDMA and NDEA.
>
> You are not determining whether or not the amount of NDMA and NDEA in the contaminated pills was or was not capable of causing cancer in the people who took them, or whether or not cancer was diagnosed in any person as a result. That is not a relevant consideration in this trial, and the parties will not be presenting evidence or making arguments intended to establish whether or not the amount of contamination in the pills was or was not capable of causing cancer in the people who took them. That issue is not relevant to the questions you will answer at the end of the case. Again, the relevant standards address whether the risk was or was not acceptable, from a regulatory standpoint.

The use of a limiting/clarifying instruction is a well-established tool to address this issue. *Branch v. Temple Univ.*, No. 21-3099, 2023 WL 3993016, at *4 (3d Cir. June 14, 2023) (affirming the trial court's use of a limiting instruction to admit evidence for specific purposes).

Review of the deposition excerpts selected by the Defendants, with the context explained, and with the foregoing principles and proposed instruction in

mind, demonstrates that there will be no prejudice to any party in applying the applicable regulatory standards.

Min Li, 322:2-8, 322:17-323:13:

This excerpt discusses the European regulatory Guidelines with regard to the Limits on Genotoxic Impurities in drugs, which was referenced in ZHP's amendment to the DMF filed in December 2013 with regard to the use of the zinc chloride manufacturing process. The language of the Guideline is phrased only in terms of "potential" and "risk."

Min Li, 329:18-331:5:

This excerpt also discusses the European regulatory Guidelines. The testimony that is designated is phrased in terms of risk, explaining that the standard thresholds relied on by ZHP do not apply to "high potency structural groups," such as n-nitroso compounds, which includes NDMA and NDEA. Min Li's responses point out that the principles were "derived from animal studies," and that this is merely stating that there is a high probability of a risk existing, thus the concept of risk is introduced, with ZHP's explanation and attempt to downplay the standards as being based on animal studies.

Min Li, 333:10-22:

This excerpt simply confirms that due to the risk, as defined with the exact phrasing in the regulatory guideline, it was not acceptable to sell the contaminated valsartan—which no Defendant disputes. This is the regulatory question at issue in this case.

Min Li, 381:13-382:17:

This excerpt discusses the ICH M7 Guideline, "Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic **Risk**." Plaintiff has withdrawn 381:20-382:4. The witness very clearly testifies that this guideline is intended to limit potential carcinogenic risk from genotoxic impurities in drugs, consistent with the title of the regulatory guideline - which is the same guideline cited by the FDA in its Warning Letter to ZHP as having particular significance in this context.

Min Li, 469:5-18:

This excerpt also addresses the M7 Guideline, which is framed in terms of risk, beginning with the title.

Min Li, 471:13-472:14:

This excerpt discusses the limits established by the FDA after ZHP finally disclosed the contamination, and the witness points out that the limits were set pursuant to the M7 guideline to limit "potential carcinogenic **risk**."

Min Li, 667:21-668:17:

This excerpt discusses the World Health Organization's Concise International Chemical Assessment Document 38 regarding NDMA, and points out that IARC classified NDMA as a probable human carcinogen based on animal study data, and the question is phrased in terms of "risks to humans as compared to animals."

Min Li, 669:11-21:

This excerpt simply confirms that NDMA and NDEA are genotoxic substances. That is the basis for their regulatory treatment.

Min Li, 685:11-687:4:

This excerpt addresses Min Li's testimony that the risk was established based on animal studies—and the witness testified that animal studies are relied on because it would be unethical to perform such studies on humans due to the risks. He points out that the same principle would apply to knowingly giving humans valsartan with the levels of contamination found in the pills here—because of the risk.

Min Li, 696:3-697:4:

This excerpt addresses a peer-reviewed scientific article cited by ZHP in its own Deviation Investigation Report, confirming the risk posed by NDMA, which is acknowledged by the witness.

Min Li, 699:24-700:11:

This excerpt confirms that, in the witness's own words (it was Min Li who introduced the concept that knowingly giving NDMA to people would be unethical), if ZHP or anyone else knowingly sold the valsartan contaminated at the levels shown in ZHP's valsartan, that would be unethical. The witness was not asked, nor did he confirm, that the NDMA in the pills at issue would cause cancer, as his testimony was framed in terms of risk.

Jucai Ge, 174:18-175:2:

This excerpt addresses one of the only studies performed regarding causation of cancer due to the contaminated valsartan pills, which the witness brought to the deposition. The question simply points out that the study authors supported the need for the recall. Plaintiffs deleted the last few words of the statement quoted out of extra caution, which stated "to protect the public health."

Peng Dong, 45:8-46:11:

This excerpt addresses the language of a 2011 ZHP internal SOP regarding the need to identify and control genotoxic impurities in ZHP's drug substances. It simply identifies the general risk of genotoxic substances, phrased in terms of "potentially" and "may." Again, this is ZHP's own SOP which was implemented to comply with the applicable regulatory cGMP rules with regard to genotoxic impurities.

Peng Dong, 370:24-371:19:

This excerpt addresses the EMA guideline on genotoxic impurities, and focuses on the regulatory framework that provided that due to the risk posed by genotoxic substances, there is no threshold applied to the amount that may be permitted as an impurity in a drug. Defendants cannot be permitted to mislead the jury into thinking that it can reject the applicability of this and the other controlling regulatory guidances if it finds that the dose of contamination in the pills was not enough to cause cancer. That is not the law.

Peng Dong, 382:14-20:

This excerpt does not include 382:18-20, which was withdrawn. It accurately describes what NDMA is. As a potent genotoxic carcinogen, NDMA impurity was required to be identified and controlled. This is the regulatory law that applies to this case.

Xiaodi Guo, 176:3-9:

This is an article written by the witness, a ZHP employee, describing the risk posed by genotoxic impurities.

Eric Gu, 366:8-16:

This excerpt addresses the November 2018 FDA Warning Letter and the root cause of the contamination—and accurately describes NDMA as a "probable human

carcinogen." Again, that is the reason for the strict regulatory treatment of NDMA and NDEA, which is the subject of the trial.

Eric Gu, 386:12-21:

This excerpt addresses the EMA guidelines relied on and known to ZHP, and accurately quotes from the guideline with regard to the category of "very potent genotoxic carcinogens" that required heightened vigilance, including NDMA and NDEA. This is all a function of risk.

Lijie Wang, 78:1-4:

This excerpt has been withdrawn.

Lijie Wang, 80:3-16:

This excerpt addresses the regulations governing genotoxic impurities. The question is phrased only in terms of risk.

Lijie Wang, 82:14-83:4, 83:17-20:

This excerpt discusses Prinston's reliance on the manufacturer, ZHP, to identify and address unsafe genotoxic impurities. If necessary, the word "unsafe" can be edited from the designation.

Lijie Wang, 152:19-153:9:

This excerpt confirms that NDMA and NDEA are within the cohort of concern of high potency mutagenic carcinogen impurities—which are not subject to the

threshold approach per the terms of the controlling regulatory guidances. The threshold approach was relied on by ZHP, and is relied on by its expert Dr. Afnan, though it was inapplicable to the most potent genotoxic impurities. These regulations establish the standards ZHP was required to comply with and use of the controlling language at trial is both reasonable and required. Injection of dose and general causation evidence by the defense in an effort to undercut the controlling legal standards should not be permitted.

Conclusion

Plaintiffs request that the Court maintain its ruling that the parties can discuss the contamination in terms of risk, precluding the legally inapplicable and irrelevant concept of causation of cancer from being introduced or relied on at trial, and instruct the jury regarding the distinction between risk and causation. The alternative suggested by the defense invites confusion and undue prejudice, and will require extensive general causation related testimony to be added back to the designations, and for the parties to call additional witnesses, lengthening and unnecessarily complicating the trial.

Respectfully,

ADAM M. SLATER

Cc: All counsel of record (via ECF)